REMARKS

The Office Action of July 28, 2004 presents the examination of claims 1-31, 46-55 and 58, claims 31-45, 56 and 57 being withdrawn from consideration following a Restriction Requirement. The present paper adds claims 59-74 . Thus, claims 1-74 are now pending.

Support for the amendments and new claims

At the urging of the Examiner during the interview, the term "vector" in the phrase "vector genome" has been replaced with another, perhaps less ambiguous term. Applicants have chosen the term "background" as described at page 12, lines 22-24 of the specification. This amendment merely substitutes a term with its definition in the specification.

New independent claim 59 recites that the chimeric glycoprotein gene or gene segment is inserted at one or more sites between the P and M open reading frames, between the N and P open reading frames, between the HN and L open reading frames or between the 3' leader sequence and the N open reading frame. This feature of claim 59 is described at, e.g. page 73, lines 27-31 of the specification.

New claim 73 recites that the expression vector comprises promoter and transcription termination sequences effective in mammalian cells or *in vitro*. Such are described at, e.g. page 59, lines 10-32.

"Antigenic domains" or "epitopes" are described at pages 40-41 of the specification. Again, at the urging of the Examiner, the term "fragments" (of a protein) has been deleted from the claims, being replaced by the better defined term, "Structural domain". "Structural domains" are described at, e.g. page 65, lines 27-30 of the specification.

"Counterpart" genes or gene segments are described at page 65, lines 24-32.

Other terms in the new claims are taken from those in the originally presented claims.

Substance of the Interview

A personal interview with the Examiner and her Supervisor was held on July 13, 2005 and a further telephone discussion with the Examiner was held later that day. Applicants wish to

thank the Examiner and her Supervisor very much for providing so much of their time to help resolve the issues in this matter.

Applicants first addressed the Collins and Klein references of record. Applicants explained that Collins (US 6,264,957) is not citable to support an obviousness rejection, being prior art only under 35 USC section 102(e) and subject to common ownership with the present application at the time the invention was made. Klein was explained as irrelevant to the present invention, being directed to producing subunit vaccines that are composed of proteins expressed in *in vitro* cultures.

Applicants presented proposed claim amendments that were considered by the Examiner and further explained how the amended claims were patentable over the Belshe reference (US 5,869,036). The Examiner or her supervisor provided some comment upon the proposed claims, such comments generally being limited to suggestions for avoiding possible rejections for lack of written description. It was acknowledged that Applicants' proposed claims, which are reflected in the claims presented in this paper and include the suggestions of the Examiner or her Supervisor, would likely be considered to distinguish the invention over Belshe.

The Examiner also agreed that claims to embodiments of chimeric viruses, immunogenic compositions comprising such viruses, isolated polynucleotides constituting the genomes of such viruses, expression vectors constituting such polynucleotides, methods for making the chimeric viruses, and methods for immunization using the viruses, would all be examined in the present application if presented.

Issues raised in the Office Action

Claims 1-10, 12, 19-23, 25, 28, 29, 46-50, 53-55 and 58 are rejected under 35 U.S.C. § 102(e) as being anticipated by Belshe et al. U.S. 5,869,036. Claims 1-30 and 46-55 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Belshe in view of Collins et al. (U.S. 6,264,957) and Klein et al. (WO93/14207). Claims 1-10, 12, 19-23, 25, 28, 29, 46-50, 53 and 54 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1-6, 8-12, 15, 16, 18-22, 24-26, 34-39 and 40 of the copending application 09/458,813.

Rejection for obviousness-type double patenting

Applicants note the provisional nature of the rejections for obviousness-type double patenting. Applicants submit that these rejections should be held in abeyance until at least one of the co-pending applications is allowed. Applicants will address any obviousness-type double patenting issues in an appropriate fashion in any particular application once one or more of the group of copending applications is allowed.

Rejection for anticipation

Claims 1-10, 12, 19-23, 25, 28, 29, 46-50, 53-55 and 58 are rejected under 35 U.S.C. § 102(e) as being anticipated by Belshe et al. U.S. 5,869,036. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Applicants have previously argued that Belshe '036 is not enabling of its disclosed embodiments and Applicants maintain their view that such is the case. However, the USPTO has made clear, in this and other applications of the Applicants, their position that concession that Belshe is not enabling of its disclosure includes an admission that the reference does not enable its claims and would therefore be invalid and that such a finding will not be made without intercession of the Board of Appeals or other higher authority than the Examining Corps.

Accordingly, Applicants provide here an explanation of the differences between the presently-claimed invention and what is disclosed by Belshe '036.

The entirety of the Belshe '036 patent relies upon extrapolation from a single kind of experiment. That is, all of Belshe's speculation comes from the result of experiments in which growth of a cp45 strain of HPIV3 at various temperatures is complemented by a plasmid expressing one or more of the NP, P and L protein of the wild-type HPIV3. This experiment is summarized in the attached Exhibit 1.

HPIV3 strain cp45 was known to exhibit a temperature sensitive phenotype for replication, such that, at 39.5 °C, the replication of the virus is nil (see Table 1 at col. 6). Complementation by a plasmid expressing wild-type HPIV3 L protein provides some very small degree of recovery of virus plaques at the non-permissive temperature; about 300 or so plaques

were formed, in comparison with the yield of 8 x 10^6 seen for the wild-type HPIV3 (compare Table 3 at col. 8 with Table 1 at col. 6).

Belshe concluded that the temperature sensitive replication phenotype of the cp45 virus was due to mutations in the L protein. From this single conclusion, Belshe et al. speculate about how a recombinant virus can be constructed.

Applicants have previously argued strenuously that Belshe does not establish any kind of expectation of success in making the "hybrid" viruses that he describes or in making the present invention. However, as to the present claims, the Examiner should consider a few things about the Belshe reference.

First, the only genome described by Belshe et al. is a non-recombinant genome of the cp45 strain. Belshe et al. do not describe any sort of recombinant genome; they mention at col. 9, lines 64-66 that Example 7 "details methods for producing attenuated hybrid vaccines for target viruses...". However, Example 7 only provides citations of papers that describe the nucleic acid sequences of various viral genes. Belshe does state at the bottom of col. 8 that, "The gene sequence which encodes the surface glycoproteins of a target virus may be substituted for the corresponding sequence in the cp45 genome which codes for the HN and F proteins, to result in a hybrid virus." However, there is no further description of how this might be accomplished. At col. 9, lines 6-19, Belshe et al. describe that a hybrid virus should contain the 3' leader of cp45, NP, P[+C] and M proteins of cp45, a sequence encoding at least one surface glycoprotein of "an enveloped target virus" and "a variant protein which is different from the L protein of wild-type HPIV 3." All of the remaining disclosure of Belshe emphasizes that the L protein of any hybrid virus must be a variant from the wild-type L protein of cp45.

At the bottom of col. 6, Belshe et al. state that changes in the neuraminidase protein provide only minor decreases in replication, by less than a factor of 10, and therefore this protein is not a major factor in the attenuation of cp45. Belshe et al. also note that perhaps changes in the 3' leader sequence are "suspected in affecting the cold adaptive, temperature sensitivity and/or attenuation phenotypes of cp45." Thus, the only significant mechanism of attenuation that Belshe discloses or suggests is mutation of the L protein to a temperature sensitive phenotype by one or more point mutations.

To summarize, Belshe et al. only describe use of a cp45 genome or antigenome, having at least two of three defined point mutations in the L protein, to obtain an attenuated HPIV3 virus. The cp45 genome is a genome of a HPIV strain. Mutation of the L protein, and perhaps (though not definitively) in the 3' leader sequence, is the only mechanism of attenuation disclosed or suggested. Belshe et al. suggest that such an attenuated HPIV3 virus might be modified by substitution of its genes encoding the HN and/or F glycoproteins with the corresponding entire genes from a "target virus" among those listed at col. 8, lines 42-58. However, as explained above, and in painstaking detail previously, Belshe et al. provide no disclosure whatsoever about how to accomplish such substitution.

On the other hand, the present claims 1 and 53 recite that a chimeric genome comprising at least one chimeric glycoprotein gene in which portions of the glycoprotein genes of two different PIV are joined. The chimeric glycoprotein gene may be added to the genome (e.g. claim 59) or substituted for one or more of the glycoprotein genes of the vector genome (e.g. claim 2). This is distinct from what is disclosed by Belshe '036, which only describes or suggests that the entirety of the HN or F genes should be exchanged between two strains of virus. The dependent claims recite a number of further features that are not at all disclosed or suggested by Belshe. For example, claim 3 recites that both ectodomain and transmembrane portions of the heterologous glycoprotein gene should be substituted for counterpart domains of the vector PIV glycoprotein genes. Claim 6 indicates that multiple chimeric glycoprotein genes should be present in the recombinant genome or antigenome. Claim 14 recites that the ectodomain of the glycoprotein of one PIV should be fused to the cytoplasmic tail of the glycoprotein gene of a second PIV. Claim 26 recites that a mutation at amino acid 456 of the L protein should be made in the recombinant genome in addition to incorporating the chimeric glycoprotein gene. None of these features is disclosed or suggested by Belshe '036.

As the invention as presently claimed is entirely distinct from what is disclosed, either expressly or inherently, by Belshe '036, the rejection of claims 1-10, 12, 19-23, 25, 28, 29, 46-50, 53-55 and 58 under 35 U.S.C. § 102(e), over Belshe et al., should be withdrawn.

This rejection should not be applied to the present claims 59-74. New claims 59-74 recite that one or more chimeric glycoprotein constructs should be inserted into the chimeric PIV

genome at one or more sites between the M and P open reading frames, the N and P open reading frames, the HN and L open reading frames or between the 3' leader sequence and the N open reading frame. Belshe '036 does not disclose this limitation, either expressly or inherently, and therefore the instant rejection should not apply to these claims.

Rejection for obviousness

Claims 1-30 and 46-55 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Belshe in view of Collins et al. (U.S. 6,264,957) and Klein et al. (WO93/14207). This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

As explained in the interview, Collins '957 is not available to the Examiner to make a rejection grounded on 35 U.S.C. § 103(a). 35 U.S.C. § 103(c). The present application was filed after November 29, 1999 and Collins '957 was assigned to the same entity, the Government of the United States of America as represented by the Department of Health and Human Services, as the present application was to be assigned at the time the present invention was made. This is evidenced by the eventual assignment of this application to that entity recorded at reel 011182, frame 0053 on September 25, 2000. Applicants' Representative notes that all of the inventors named on this application were employees of the National Institutes of Health and had an obligation, via an employment agreement, to assign their rights in the present invention to the Government of the United States of America as represented by the Department of Health and Human Services at the time the invention was made. Applicants will present evidence of such employment agreements at the request of the Examiner.

As was also explained in the interview, Klein '207 is not at all relevant to the present invention. It is true that Klein et al. describe making chimeric antigens, for example a chimera of a glycoprotein of a PIV with a glycoprotein of RSV. However, this disclosure of Klein '207 is made in the context of expressing the chimeric protein as a heterologous protein from a eukaryotic host cell in culture. See, for example, Examples 5-7, beginning at page 18 of the reference, describing expression of F_{PIV3}-F_{RSV} chimeric glycoprotein F from a baculovirus vector in Sf9 cells.

Such disclosure is remote from the present invention, in which a genome for a live, infectious, chimeric parainfluenza virus is constructed. Though perhaps providing description of what might be an interesting gene for an antigen to include in a genome of a live, chimeric PIV, Klein '207 tells one of ordinary skill in the art nothing at all about any other feature of the present invention, nor anything about how to make or use the present invention.

As the Collins reference of the combination is not available to the Examiner, Applicants submit that the present invention is not *prima facie* obvious over Belshe '036 or Belshe '036 combined with Klein.

As explained above, Belshe '036 only discloses substitution of the complete HN or F gene of one virus by the complete HN or F gene of another virus. Belshe '036 does not disclose or in any way suggest that glycoprotein genes should be chimerized in the making of a chimeric HPIV. Furthermore, even if such a suggestion were present, Belshe '036 does not disclose any way that such a chimeric glycoprotein gene could be formed and then incorporated into a recombinant genome or antigenome of a HPIV. There is no motivation provided by the reference, or by the state of the art at the time the invention was made, to join gene segments encoding different parts of HPIV glycoproteins and to incorporate such a chimeric glycoprotein gene into a HPIV virus.

Thus, the present invention is not obvious in view of Belshe '036 alone.

Klein '207 makes no disclosure that an infectious, chimeric PIV should incorporate a genome including chimeric glycoprotein genes. The combination of Klein '027 with Belshe '036 still leaves the Examiner yet to explain specifically how the combined references (or the state of the art at the time the invention was made) meet the requirement of providing some suggestion that a chimeric glycoprotein gene should be incorporated into an infectious, recombinant PIV. The combined references are also deficient in that there still remains no teaching of how to incorporate any chimeric glycoprotein gene into a recombinant infectious PIV virus. Accordingly, Klein '207 does not remedy the deficiency of Belshe '036 to establish *prima facie* obviousness of the presently-claimed invention and the present invention is not obvious over Belshe '036 in view of Klein '207.

For the above reasons, the rejection of claims 1-30 and 46-55 under 35 U.S.C. § 103(a) as being unpatentable over Belshe in view of Collins et al. (U.S. 6,264,957) and Klein et al. (WO93/14207) should be withdrawn.

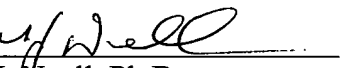
Furthermore, the combination of Belshe '036 with Klein '207 does not describe or suggest that a chimeric glycoprotein gene should be inserted into the genome or antigenome of a live, infectious PIV as an additional gene at a site between the M and P open reading frames, the N and P open reading frames, the HN and L open reading frames or between the 3' leader sequence and the N open reading frame. Therefore the instant rejection should not apply to new claims 56-74.

The present application well-describes and claims patentable subject matter. The favorable action of allowance of the pending claims and passage of the application to issue is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell (Reg. No. 36,623) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Dated: August 26, 2005

Respectfully submitted,

By 

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